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Does Fetal Growth Restriction Cause Later Obesity?
Pitfalls in Analyzing Causal Mediators as Confounders

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ABSTRACT

Recent studies reporting that small-for-gestational-age (SGA) birth is associated with increased adiposity in childhood and adulthood have been based on analyses “adjusting” for height, weight, or BMI measured concurrently with the adiposity measurement. To assess the potential for bias due to overadjustment for a causal mediator, we compared two approaches to analyzing the association between SGA birth and adiposity outcomes (skinfold thicknesses and bioelectrical impedance measure of body fat) at age 11.5 years using the same dataset on a cohort of Belarusian children followed from birth in 1996-97: (1) effect of SGA birth on adiposity, adjusted for baseline covariates only; and (2) additional regression adjustment for concurrent height, weight, or BMI. The first approach yielded negative associations between SGA birth and all adiposity outcomes. Regression modeling of concurrent weight or BMI reversed (i.e., to positive) the SGA-adiposity association. To explore the latter anthropometric measures as causal mediators, we also used marginal structural models (MSMs) to estimate the controlled direct effect of SGA birth. That effect was similar to the effect seen with the first approach when modeled on height, was null when modeled on BMI, but was confounded by differences in lean vs fat mass when modeled on weight.

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Key words: obesity; causal inference; lifecourse epidemiology; bias; marginal structural models

Abbreviations:

SGA = small for gestational age

AGA = appropriate for gestational age

BMI = body mass index

PROBIT = Promotion of Breastfeeding Intervention Trial

MSM = marginal structural model

Epidemiologic studies published from the 1970s to the 1990s reported that infants born small for gestational age (SGA)-experienced long-term reductions in height, weight, body mass index (BMI), and skinfold thicknesses.(1-5) Several recent studies, however, have reported that SGA birth is associated with **greater** adiposity in later childhood and adulthood, suggesting a fetal origin of obesity(6-8) and a link to adult chronic disease outcomes that have also been associated with restricted fetal growth, including high blood pressure, type 2 diabetes, and coronary heart disease.(9)

In a recent publication(10) based on 11.5-year-old Belarusian children followed from birth, we reported results for the SGA-adiposity association that were consistent with the older(1-5) and some recent(11-17) epidemiologic literature, but contrasted with the above-cited studies.(6-8) We hypothesized(10) that the contrasting results were caused by the latter(6-8) studies' overadjustment of adiposity measurements for height, weight, and/or BMI obtained at the same time as the adiposity measurements. In the current paper, we illustrate the pitfalls of analyzing these anthropometric mediators as confounders by using alternative statistical approaches to the same longitudinal dataset.

METHODS

We present observational analyses of Belarusian children who participated in the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster-randomized trial of a breastfeeding promotion intervention. The original design of PROBIT(18) and a description of the follow-up anthropometric methods and results at 11.5 years(19) have been previously published. In brief,

the clusters randomized were 31 maternity hospitals and one affiliated polyclinic (an outpatient clinic where children receive routine health care) per hospital. The trial recruited 17,046 healthy, singleton infants with gestational age ≥ 37 weeks (92.5% ultrasound-confirmed), birth weight ≥ 2500 grams, and 5-minute Apgar scores ≥ 5 . All were born in 1996 and 1997, were enrolled during their postpartum stay, and initiated breastfeeding.

Follow-up interviews and examinations at 6.5 and 11.5 years of age were performed by one or two pediatricians (depending on volume) at each of the 31 affiliated polyclinics. The training and quality-assurance procedures at both the 6.5- and 11.5-year follow-up visits have been described in detail previously.(19;20) The 11.5-year follow-up included measurements of height, weight, waist and hip circumferences, triceps and subscapular skinfold thicknesses, and percentage body fat, based on foot-to-foot bioelectrical impedance using the Tanita TBF body fat analyzer. This measure of body fat has been found to correlate extremely highly with body fat mass measured by dual-energy x-ray absorptiometry in school-age children.(21) We excluded *a priori* children with implausible outcome measurements, i.e., those with values < -4 SD ($n = 0-2$, depending on measurement) or $> +4$ SD ($n = 3-117$) from the mean.

For simplicity and clarity, the current analysis is limited to comparisons of infants born SGA and those born appropriate for gestational age (AGA), i.e., it excludes infants born large for gestational age, who are known to be at higher risk for later obesity. SGA birth was defined as a birth weight $< 10^{\text{th}}$ percentile for gestational age and sex, derived from a Canadian population-based reference(22) (no such reference is available for Belarus). AGA birth was defined as birth weight between the 10^{th} and 90^{th} percentiles of the same reference.

To illustrate the pitfalls of analyzing mediators as confounders, we analyzed the same dataset using two different statistical approaches. The first approach (already reported)(10) estimates the total effect of SGA on adiposity at 11.5 years, i.e., it does not adjust for any of the anthropometric mediators measured at the 11.5-year follow-up. The approach is based on the MIXED procedure in SAS (version 9.4; SAS Institute, Inc.), which accounts for the clustered measurement of the adiposity outcomes (by polyclinic) and adjusts for the following potentially confounding baseline covariates: maternal and paternal height and BMI, geographic region, urban vs rural residence, and maternal education. To maximize precision, we also adjusted for the child's exact age at follow-up. Because the breastfeeding promotion intervention had no effect on any of the adiposity outcomes,(18) we did not adjust for intervention group. The second approach uses regression modeling in an attempt to estimate the independent effect of SGA on 11.5-year adiposity by adjusting for the concurrent anthropometric mediators as if they were confounding factors.(23) For this approach, we used the same MIXED procedure in SAS and the same baseline confounders but also included either height, weight, or BMI measured at 11.5 years of age.

Finally, we also used marginal structural models (MSMs) to explore causal pathways from SGA birth to child adiposity via the anthropometric mediators. Unlike the two approaches to estimating the causal effect of SGA birth on child adiposity, the MSM estimates the controlled direct effect, i.e., the effect of SGA birth that is not mediated by the concurrent anthropometric measures.(24) The MSM was also fit using the MIXED procedure in SAS, using inverse probability weighting of the mediators.(24-26) The weights for continuous variables were calculated using the procedures reported by Cole and Hernán.(27;28) We estimated two sets of

weights: one for exposure (SGA vs AGA birth) and one for each of the three anthropometric mediators. The inverse probability weight for SGA birth was calculated from a logistic regression model including the baseline covariates, while the weight for the mediator was based on a linear regression model including the same baseline covariates, exposure, and mediator. Weights for both exposure and mediator were stabilized by replacing the numerator with the marginal probability of the observed exposure, and the marginal probability of the observed intermediate conditional on the exposure, respectively.(27;28) In addition, the stabilized weights were truncated at the 1st and 99th percentiles.(27) We used the product of the two stabilized weights for the exposure and mediator for the inverse probability weighting in the MSM to estimate the controlled direct effect.(24-26)

RESULTS

Table 1 summarizes the baseline characteristics of the SGA and AGA newborn infants who were followed up at age 11.5 years. As expected, small but statistically significant differences were seen in place of residence and maternal education between the SGA and AGA groups, with larger, highly statistically significant differences in maternal and paternal height and BMI.

Table 2 shows the mean (\pm SD) height, weight, BMI, and adiposity outcomes in the SGA and AGA groups. As previously reported,(10) all of these measurements were significantly lower in the SGA group than in the AGA group, with the exception of the subscapular:triceps ratio, which was slightly but significantly higher in the SGA than in the AGA group.

In Table 3, we compare the two statistical approaches to estimating the causal effect of SGA (vs AGA) birth on the adiposity outcomes. With the exception of the subscapular:triceps ratio, effects observed in the first approach were reduced when using the second (regression modeling to adjust for concurrent height), and were reversed when adjusted for concurrent weight or BMI. Finally, Table 4 shows the controlled direct effects from the MSM. Those effects were similar to the total effects from the first approach with height as the mediator and similar to those of regression modeling with weight as the mediator (see Table 3). They were close to null, however, with BMI as the mediator.

DISCUSSION

We observed substantial differences among the two compared statistical approaches. These contrasting results were obtained using the same dataset and controlled for the same set of potentially confounding baseline covariates (see Table 1), all of which temporally preceded both exposure and outcome. Our findings demonstrate that different statistical approaches to analysis of anthropometric measurements affected by SGA birth and obtained concurrently with the adiposity outcomes can yield opposite results and causal inferences. Our findings cannot be explained by differences in study setting, the exclusion of infants weighing <2500 grams at birth, or restriction to infants who initiated breastfeeding—the explanations offered by the editorial that accompanied our previous manuscript(29)—since these were identical under both approaches.

Why are the results of these two analytic approaches so different? Regression adjustment for the mediator biases the effect estimate by overadjusting for concurrent height, weight, or BMI as if it

were a confounder.(30-32) A true confounder, however, should be a cause of exposure (here, SGA birth) and thus temporally precedent to it.(30) This is quite different from a causal mediator, which by definition occurs after the exposure and is itself a consequence of exposure. Neither height, weight, nor BMI at age 11.5 years can influence fetal growth (SGA vs AGA birth). If it were possible to randomize human fetuses to become SGA vs AGA newborns, no trialist would “adjust” for post-randomization outcomes, because those outcomes are potentially caused by the randomized intervention. Similarly, adjusting for an effect of exposure in an observational study will systematically bias the estimate of its effect on-outcomes that occur “downstream” from the mediator adjusted for. To the extent that effect on the mediator adjusted for is in the same direction as, and lies on the causal path to, the downstream outcomes, effect estimates for the latter outcomes will be biased downwards or even reversed.(31;32)

Why should an investigator be interested in effects of SGA birth on adiposity that are “independent” of its effects on concurrent height, weight, or BMI? In a nutritional or biological context, it is not clear what such “independent” effects denote. Adjusting for height is like selecting those SGA infants who catch up to AGA infants in stature. SGA-born children who catch up in height are also likely to catch up in adiposity to those in the AGA group, and most of the overall (total) effect of SGA on adiposity is consequently removed (overadjusted). Adjusting for weight creates even greater bias. On average, SGA-born children are shorter than their AGA counterparts(10); thus their average BMI is higher at the same weight.

We explored causal pathways from SGA birth to child adiposity by using MSMs. MSMs estimate the controlled direct effect of SGA birth: the effect of SGA birth when the concurrent

anthropometric mediator is held constant, i.e., the unmediated effect. The inverse probability weighting of the intermediate removes the association between the intermediate and the exposure in the resulting pseudo-population. Using height as the mediator in the MSM yields controlled direct effects similar to the total effect of the baseline-only approach, demonstrating that the negative effect of SGA on later adiposity operates independently of its negative effect on height. Using BMI as the mediator in the MSM model also appears to provide a valid inference for the null controlled direct effect by suggesting that the negative effect of SGA birth on later adiposity is largely indirect, i.e., it is similar to its negative effect on BMI. These results suggest that similar BMIs among children born SGA vs AGA in the pseudo-population ensure similar fat:lean ratios.

Even the MSM modeling approach, however, assumes no uncontrolled confounding of the mediator-outcome association. Although the MSM with weight as mediator ensures no association between weight and SGA in the pseudo-population, it is not immune to confounding by the inverse association between height and BMI at a given weight, i.e., between lean mass and fat mass. This source of confounding also contributes to the biased results of the regression (second) approach with weight as the mediator.

These considerations make it clear that the first statistical approach, which estimates the total effect of SGA birth on adiposity, is clearly preferred to the second. True (baseline) confounders of the exposure-outcome association are taken into account. The second approach, however, attempts to estimate an “independent” effect by treating-concurrent anthropometric mediators as confounders using regression modeling, as has been done in some recent studies.(6-8) MSM

estimation of controlled direct effects provides insight about causal pathways when adjusting for height or BMI but, as with regression modeling, induces confounding by lean vs fat mass when adjusting for weight.

Our findings have important implications for other outcomes studied in lifecourse epidemiology. Longitudinal (cohort) studies have many methodologic advantages for studying long-term effects of early-life exposures, but ensuring temporal precedence of potential confounders and appropriate analysis of causal mediators is essential to avoid overadjustment and biased causal inferences.

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Conflicts of Interest:

None.

Table 1. Baseline characteristics of PROBIT children born SGA or AGA

Characteristic	SGA (n = 1,247)	AGA (n = 11,560)	P value^a
Place or residence	%	%	<0.001
East/urban	33.4	31.8	
East/rural	16.2	15.4	
West/urban	21.2	26.5	
West/rural	29.2	26.2	
Maternal education	%	%	<0.001
Completed university	10.0	13.8	
Partial university	47.5	51.2	
Completed secondary school	37.4	31.4	
Incomplete secondary school	5.1	3.6	
	Mean (SD)	Mean (SD)	
Maternal height (cm) ^b	162.4 (5.9)	164.1 (5.7)	<0.001
Maternal BMI ^b	25.3 (5.2)	26.5 (5.5)	<0.001
Paternal height (cm) ^b	174.9 (6.8)	176.0 (6.6)	<0.001
Paternal BMI ^b	25.2 (3.3)	25.7 (3.2)	<0.001

^a Based on chi-square tests for comparisons of proportions and t-tests for comparisons of means

^b Based on heights and weights reported by the mother at the 6.5-year visit

SD = standard deviation; SGA = small for gestational age; AGA = appropriate for gestational age; SF = skinfold; BMI = body mass index in kg/m²

Table 2. Crude comparison of anthropometric mediators and adiposity outcomes in 11.5-year-old children born SGA vs AGA

Anthropometric Mediators	SGA	AGA	P Value^a
	Mean (SD)	Mean (SD)	
Height (cm)	147.4 (8.0)	149.8 (7.7)	<0.001
Weight (kg)	38.2 (8.6)	41.1 (9.2)	<0.001
BMI	17.4 (2.8)	18.1 (2.9)	<0.001
Adiposity Outcomes			<0.001
Percent body fat	15.8 (7.6)	17.1 (7.8)	<0.001
Fat mass index (kg/m ²)	2.9 (1.8)	3.3 (2.0)	<0.001
Triceps SF thickness (mm)	12.8 (6.0)	13.9 (6.3)	<0.001
Subscapular SF thickness (mm)	8.3 (4.6)	8.9 (5.0)	<0.001
Sum of SFs (mm)	21.1 (10.1)	22.9 (10.8)	<0.001
Subscapular:triceps ratio	0.68 (0.27)	0.66 (0.22)	0.009

^a Based on t-tests of differences in means

SD = standard deviation; SGA = small for gestational age; AGA = appropriate for gestational age; BMI = body mass index in kg/m²; SF = skinfold

Table 3. Effect estimates (and 95% CIs) for adiposity measures at 11.5 years in the SGA (vs AGA) groups using two different statistical approaches

Outcome	Baseline Covariates ^a Only		Baseline Covariates ^a + Anthropometric Mediators					
	Effect Estimate	95% CI	Height		Weight		BMI	
			Effect Estimate	95% CI	Effect Estimate	95% CI	Effect Estimate	95% CI
Percentage body fat (%)	−0.5	−1.0, +0.1	0.0	−0.5, +0.5	+0.6	+0.3, +0.9	+0.4	+0.1, +0.7
Fat mass index (kg/m ²)	−0.2	−0.3, −0.05	−0.1	−0.2, +0.1	+0.1	+0.1, +0.2	+0.1	+0.04, +0.2
Triceps SF (mm)	−0.6	−1.0, −0.2	−0.3	−0.7, +0.1	+0.1	−0.1, +0.4	0.0	−0.2, +0.3
Subscapular SF (mm)	−0.2	−0.5, +0.1	0.0	−0.3, +0.3	+0.5	+0.2, +0.7	+0.4	+0.2, +0.6
Sum of SFs (mm)	−0.8	−1.5, −0.1	−0.3	−1.0, +0.3	+0.5	+0.1, +1.0	+0.3	−0.1, +0.8
Subscapular:triceps ratio	+0.02	+0.01, +0.04	+0.03	+0.01, +0.04	+0.03	+0.02, +0.04	+0.03	+0.02, +0.04

^a Both approaches include adjustment for the baseline covariates shown in Table 1

CI = confidence interval; SGA = small for gestational age; AGA = appropriate for gestational age; BMI = body mass index; SF = skinfold

Table 4. MSM estimates (and 95% CIs) of the controlled direct effect of SGA birth on adiposity measures at 11.5 years, with mediation by height, weight, or BMI

	MSM Controlled Direct Effect ^a					
	Height		Weight		BMI	
	MSM Estimate	95% CI	MSM Estimate	95% CI	MSM Estimate	95% CI
Percentage body fat (%)	−0.6	−1.0, −0.1	+0.5	+0.2, +0.8	0.0	−0.3, +0.2
Fat mass index (kg/m ²)	−0.2	−0.3, −0.1	+0.1	+0.1, +0.2	0.0	−0.05, +0.1
Triceps SF (mm)	−0.4	−0.7, −0.05	+0.4	+0.1, +0.6	0.0	−0.3, +0.2
Subscapular SF (mm)	−0.2	−0.5, +0.1	+0.5	+0.3, +0.7	+0.2	+0.03, +0.4
Sum of SFs (mm)	−0.6	−1.2, +0.01	+0.8	+0.4, +1.2	+0.2	−0.2, +0.6
Subscapular:triceps ratio	+0.01	+0.003, +0.03	+0.02	+0.01, +0.04	+0.02	+0.01, +0.03

^a Includes adjustment for the baseline covariates shown in Table 1

CI = confidence interval; SGA = small for gestational age; MSM = marginal structural model; BMI = body mass index; SF = skinfold

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